

Biceps tendinitis in chronic rotator cuff tears: A histologic perspective

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Patients with chronic rotator cuff tears frequently have anterior shoulder pain attributed to the long head of the biceps brachii (LHBB) tendon. In this study, tenodesis or tenotomy samples and cadaveric controls were assessed by use of immunohistochemical and histologic methods to quantify inflammation, vascularity, and neuronal plasticity. Patients had moderate pain and positive results on at least 1 clinical test of shoulder function. The number of axons in the distal LHBB was significantly less in patients with biceps tendinitis. Calcitonin gene-related peptide and substance P immunostaining was predominantly within nerve roots and blood vessels. A moderate correlation ($R = 0.5$) was identified between LHBB vascularity and pain scores. On the basis of these results, we conclude that, in the context of rotator cuff disease, the etiology of anterior shoulder pain with macroscopic changes in the biceps tendon is related to the complex interaction of the tendon and surrounding soft tissues, rather than a single entity. (J Shoulder Elbow Surg 2008;17:898-904.)

To date, the functional role of the long head of the biceps brachii (LHBB) tendon and an effective treatment algorithm for pathology have yet to be elucidated. Though once considered a vestigial structure of the shoulder,¹⁷ several biomechanical studies in cadaveric models have asserted that the LHBB is an anterior and superior stabilizer of the glenohumeral joint.^{16,22,25,32} This function of the LHBB tendon is alleged to be more important in rotator cuff-deficient

shoulders than intact constructs.⁴ Conversely, shoulder function and stabilization are minimally affected in cases of LHBB tendon rupture or surgical removal.^{18,29} These functional interpretations are not without controversy.

The role of the LHBB tendon as a source of anterior pain in the shoulder is widely accepted.^{12,27} This pain is frequently elicited through the palpation of the anterior shoulder but can also be detected through Speed's²⁰ and Yergason's³³ tests. Chen et al⁷ showed significant correlation between rotator cuff tears and biceps pathology, with all chronic tears (>3 months) having some degree of macroscopic biceps abnormality. Further cadaveric studies identified morphologic alterations (cross-sectional area widening) between biceps tendons from shoulders with normal and torn rotator cuffs.³¹ Anterior shoulder pain with a rotator cuff tear is a relative indication for the removal of the proximal LHBB tendon from within the shoulder joint and bicipital groove with subsequent tenodesis or simple tenotomy.

Despite its documented association with pain, the decision to remove the LHBB tendon is difficult because arthroscopic examination of the tendon rarely shows gross pathology.

Previous work by Murthi et al¹⁹ describes the histopathology of the LHBB tendon in shoulders undergoing arthroscopic subacromial decompression for impingement syndrome, whereas Kannus and Jozsa¹³ have reported on degenerative changes in ruptured biceps tendons. There are otherwise limited histopathologic information data on the LHBB tendon, especially in cases of chronic rotator cuff tears.

Tendon vascularity and innervation are thought to contribute to the histopathology and symptomatology of chronic injury. Tendinosis of the elbow has been correlated with vascular hyperplasia and disorganization.¹⁵ Studies by Alpantaki et al³ suggest the presence of sensory and autonomic neuropeptides more in the proximal end of the LHBB tendon. Ackermann et al² showed that the ruptured Achilles tendon in a rat model expressed calcitonin gene-related peptide (CGRP), a marker for sensory nerve fibers.

Previous work correlated the presence of bicipital pathology to larger cuff tears and less favorable outcomes of rotator cuff reconstruction, although the

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microscopic characteristics of the tendon were not elucidated.⁵ Given the natural history of pain relief after biceps tenodesis or tenotomy, a histologic study of biceps tendons obtained from such surgical procedures may provide further insight into potential tissue features associated with pain. The purpose of this study was to determine intrinsic changes of the LHBB tendon and its sheath in subjects with concomitant rotator cuff tears through histology and immunohistochemistry. The histologic findings were correlated with results from clinical tests of the patients from whom biopsy tissue was obtained.

MATERIALS AND METHODS

All procedures were approved by the institutional review board. The study was carried out by use of a histologic analysis of the biceps tendon and its sheath in 2 separate phases. Phase 1 consisted of histologic analysis of biopsied LHBB tendons by use of Masson's trichrome stain and immunohistochemistry for CGRP and substance P. In the second phase, the role of the LHBB tendon sheath was analyzed via routine hematoxylin-eosin staining, and histologic scores were correlated to diagnostic examinations for biceps tendinitis by use of appropriate statistical tests.

Phase 1: Evaluation of tendon

Surgical specimens of the LHBB were collected from 6 subjects undergoing arthroscopically assisted biceps tenodesis. The mean patient age was 51 years (range, 44-60 years), with 3 men and 3 women. Control tendons were collected from 6 cadavers from the Gift of Hope Organ and Tissue Donor Network (Elmhurst, IL). Before being included in the control group, cadaveric specimens were examined for (1) healed incisions or scars, (2) rotator cuff tearing or degeneration, and (3) any evidence of labral or capsular pathology. Any abnormalities resulted in exclusion from the study. The mean age of the cadavers was 76 years (range, 42-81 years), with 5 men and 1 woman.

Informed consent was obtained from the patients before a brief history was taken and physical examination performed. The history included duration of injury and symptoms, hand dominance, other known shoulder pathologies, prior treatments, and pain assessment by use of a visual analog scale (VAS) for pain (where 0 indicates no pain and 10 indicates severe pain). The focused physical examination included Yergason's test,³³ Speed's test,²⁰ O'Brien's sign, and the crank test.

At the time of arthroscopy, the intra-articular LHBB tendon was visually inspected for pathology, including inflammation, fraying, and tearing. Concurrent pathologies, if applicable, were included in the surgical assessment of the LHBB tendon.

The portion of the LHBB tendon above the bicipital groove was surgically harvested from each of the 6 subjects. The orientation of the intra-articular tendon was marked, and the 0.5 cm closest to both ends was immersed in Zamboni's fixative (8% paraformaldehyde, 0.4-mol/L phosphate buffer, 1.5% saturated picric acid) for 24 hours. Zamboni's fixative was selected for its ability to preserve antigenicity for immu-

Table 1 Clinical examination results for phase 1

Test	Positive	Negative
Yergason's test	33%	67%
Speed's test	83%	17%
Anterior shoulder point tenderness	100%	0%
O'Brien's test	83%	17%
Crank test	100%	0%

Data are given as percentage of patients with respective outcome.

nohistochemistry.^{1,28} The samples were then rinsed and stored in 20% sucrose and 0.1-mol/L Sorensen's buffer (pH 7.2). Proximal and distal halves of the samples were paraffin embedded, sectioned to 8 μ m, and stained with Masson's trichrome stain. The most proximal and distal sections of the LHBB were assessed by 2 independent observers for mean number of axons and blood vessels per microscopic field.

For immunohistochemical analysis, the sections were deparaffinized and washed in distilled water and phosphate-buffered saline solution. Endogenous peroxidase activity was blocked with 2% hydrogen peroxide; nonspecific binding of the antibodies was blocked with 10% normal goat serum. Polyclonal rabbit anti-CGRP (Abcam, Cambridge, MA), with 1:100 dilution, and polyclonal rabbit anti-substance P serum (Phoenix Pharmaceuticals, St Joseph, MO), with 1:200 dilution, were used as the primary antibodies. Horseradish peroxidase-biotinylated goat anti-rabbit antibody was used as a secondary antibody, with 1:20 dilution, in 1% bovine serum albumin in phosphate-buffered saline solution. Immunohistochemical analysis was performed by 2 independent observers under light microscopy. To demonstrate specificity of the staining, rat vertebra (cervical), containing nerve roots and blood vessels, was used as a positive control. Negative controls contained no primary or secondary antibodies. To confirm the pattern, immunohistochemistry was repeated with another anti-CGRP antibody (Chemicon International, Temecula, CA). The specificity of the anti-substance P was confirmed in an earlier publication.⁸

Phase 2: Evaluation of tendon sheath

Surgical specimens, including the LHBB and tendon sheath, were collected from 8 additional patients undergoing arthroscopically assisted biceps tenodesis with concomitant arthroscopic rotator cuff repair. The mean age of the patients was 52 \pm 11 years (range, 32-70 years), with 6 men and 2 women. For control tissues, 8 fresh-frozen biceps tendons from specimens with an intact rotator cuff were obtained from the Orthopaedic Learning Center (Rosemont, IL). The mean age was 73 \pm 8 years (range, 65-85 years), with 4 men and 2 women. The age and gender of 2 control samples were unavailable. Preoperative and perioperative analyses were undertaken in a manner consistent with those described for phase 1 of the project.

A sample of the proximal, intra-articular LHBB tendon and sheath was collected before arthroscopically assisted tenodesis. The specimen was fixed in 10% neutral buffered formalin for 7 days before paraffin embedding and sectioning to

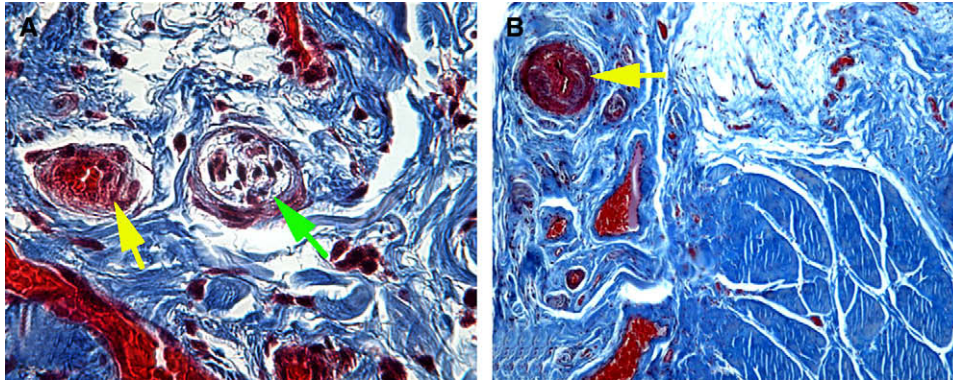


Figure 1 **A**, Masson's trichrome stain of cadaveric tendon (control). The *green arrow* indicates nerve roots; the *yellow arrow* indicates blood vessels. (Original magnification $\times 200$.) **B**, Masson's trichrome stain of surgical specimens (experimental). The *yellow arrow* indicates blood vessels. (Original magnification $\times 200$.)

8 μm . Hematoxylin-eosin-stained sections were evaluated for inflammation by 3 blinded observers using the following grading scale: grade 0, normal staining without any inflammatory cells; grade 1, slight thickening of the sheath; grade 2, thickening of the sheath and mild inflammation; grade 3, thickening of the sheath and moderate inflammation; and grade 4, thickening of the sheath and marked inflammation.

Similarly, vascularity of the tendon sheath was graded on a scale from 1 to 4 by use of a modification of a previously published scoring system³⁰ (where 1 indicates inconspicuous blood vessels and 4 indicates marked vascular response).

Statistics

A Mann-Whitney test was performed to compare the histologic scores of the surgical samples and the controls. Statistical correlations were also performed to determine relationships between the clinical and histologic scores (Pearson test for pain score and χ^2 analysis for Yergason's and Speed's tests). $P < .05$ was considered significant in all tests. Post-test statistical power was computed by use of Statistica software, version 5.5 (StatSoft, Tulsa, OK).

RESULTS

Phase 1: Evaluation of tendon

The right shoulder was affected in 4 of 6 patients, all right hand dominant. All had complaints of chronic pain (ie, >12 months) in activities of daily living, with a mean VAS score of 7.8 on a scale from 0 to 10 (with 10 being the greatest pain the patient has experienced). Physical examination findings are summarized in Table I.

All affected LHBB tendons were macroscopically inflamed, and one presented with additional tenosynovitis. No subjects had biceps tendon dislocation or tears. Four had concurrent rotator cuff tears, one had a previous rotator cuff repair, and one lacked significant rotator cuff pathology. The labrum was degener-

ative in two. One had a focal chondral defect of the humeral head.

Histologically, the mean number of axons in the control specimens was 4.5 ± 4.1 (range, 0-12) proximally and 5.8 ± 4 (range, 3-13) distally. The surgical specimens had fewer mean axons per cross-sectional area, with 3.8 ± 3.7 (range, 1-10) proximally and 1.2 ± 1.3 (range, 0-3) distally (Figure 1). The difference between the 2 groups was statistically significant ($P = .04$) distally, but no statistical difference was noted proximally.

The surgical specimens showed fewer blood vessels proximally compared with the control LHBB tendon specimens, with a mean of 4.4 ± 2.8 blood vessels per microscopic field (range, 1-7) compared with 5.6 ± 2.9 (range, 1-9) in the controls. Similarly, the mean number of blood vessels at the distal end for the surgical specimens and controls was 2.8 ± 1.1 (range, 1-4) and 6.3 ± 3.9 (range, 2-11), respectively. The greater number of blood vessels in the control specimens was not statistically significant at either end ($P = .30$ proximally and $P = .17$ distally). The statistical power of these comparisons ranged between 0.4 and 0.6.

The immunohistochemical staining detecting CGRP and substance P was found globally throughout the tendon body in the proximal and distal sections of both groups (Figure 2). The relative intensity, as determined through subjective scoring, provided no significant differences between the control and experimental tendons. The highest levels of both proteins were observed in the positive controls (rat cervical vertebrae), with lesser staining in both experimental sections and control (cadaveric) specimens.

Phase 2: Tendon sheath

The left shoulder was affected in 6 of 8 patients, and all were right hand dominant. All had complaints of chronic pain (ie, >12 months), with a mean VAS

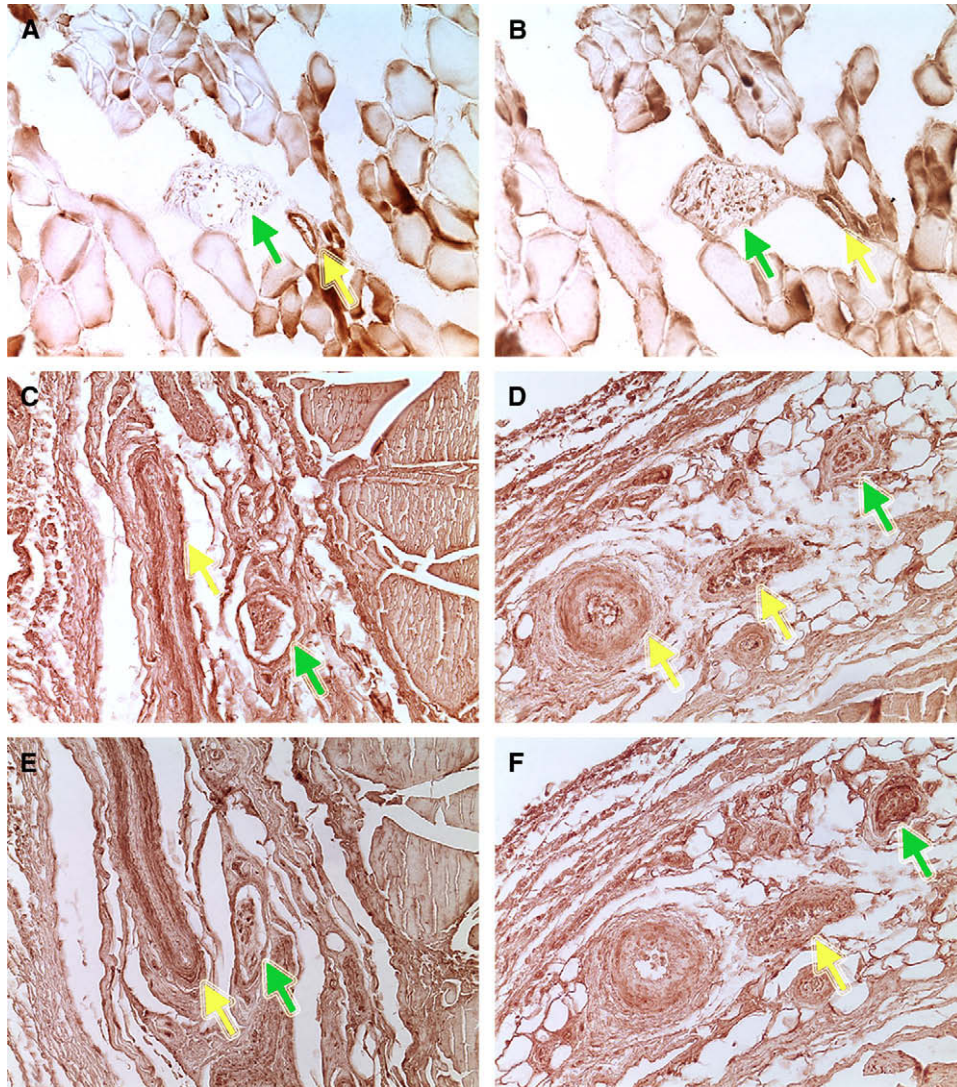


Figure 2 Immunostaining with CGRP antibodies (**A**, **E**, and **F**) and substance P antibodies (**B**, **C**, and **D**). **A** and **B**, Positive controls: sections of cervical part of vertebra from normal rat with presence of nerve root and blood vessel. **C** and **E**, Control tendons. **D** and **F**, Experimental samples. *Green arrows indicate nerve roots; yellow arrows indicate blood vessels.* (Original magnification $\times 200$.)

score of 5.6 ± 1.3 (range, 4-8). The elicited physical examination findings are summarized in Table II.

On arthroscopic evaluation, 5 of 8 patients had biceps tendinitis, with 1 associated case of capsulitis. A frank biceps tear was identified in 1 patient. There was no consistent relationship between the clinical tests and the arthroscopic findings for biceps tendinitis. All patients underwent arthroscopic rotator cuff repair, whereas 1 underwent combined rotator cuff and superior labrum anterior-posterior repairs.

The mean histologic scores for inflammation and vascularity were 1.1 ± 1.3 and 2.0 ± 1.1 , respec-

tively, in the surgical samples and 0.4 ± 0.6 and 1.2 ± 0.3 , respectively, in controls. The Mann-Whitney test showed no significant differences in either inflammation ($P = .26$) or vascularity ($P = .13$) between the surgical samples and the controls. The statistical power of these comparisons was 0.47 to 0.54.

With respect to pain scores, inflammation showed no correlation ($R < 0.1$) whereas vascularity showed a moderate correlation ($R = 0.5$). χ^2 Analysis failed to show a relationship between Yergason's ($P = .34$) and Speed's ($P > .9$) tests and the histologic grades for either inflammation or vascularity.

Table II Clinical examination results for phase 2

Test	Positive	Negative
Yergason's test	75%	25%
Speed's test	50%	50%
Anterior shoulder point tenderness	75%	25%
O'Brien's test*	85.7%	14.3%
Crank test*	42.8%	57.2%

Data are given as percentage of patients with respective outcome.

*Could not be performed in 1 patient.

DISCUSSION

The LHBB tendon has been identified as a significant source of anterior shoulder pain despite the lack of visible intra-articular pathology.^{17,22} This has been found to be especially true in shoulders with concurrent soft-tissue pathology (eg, rotator cuff tears, labral tears, and cartilage degeneration). Removal of the LHBB tendon with arthroscopically assisted tenodesis has consistently provided appropriate pain relief and maintained biceps muscle function.

This study histologically evaluated the LHBB tendon from patients with chronic rotator cuff tears. Previous work by Murthi et al¹⁹ focused on patients who underwent arthroscopy for subacromial impingement or rotator cuff pathology. The degree of rotator cuff pathology correlated with the incidence of bicep pathology, namely chronic inflammation. All patients receiving tenodesis had macroscopic degeneration of the LHBB tendon, although only 49% were visible arthroscopically. Given this inherent difficulty in visualizing biceps pathology, we sought to correlate standard examinations with the presence of microscopic alterations.

During phase 1 of the study, we hypothesized that the biceps tendons from our experimental group would show histologic evidence of inflammation and the presence of CGRP, a nociceptive neuropeptide, whereas the control group would not. Substance P and CGRP immunoreactivity increases in the nerve endings of inflamed tissues; thus, they were selected as markers of pathologic changes of the LHBB.^{8,9,24} In addition, immunoreactive fibers have been noted to be localized in close proximity to blood vessels.¹⁰ Onuoha and Alpar²¹ noted an increase in circulating substance P and CGRP after soft-tissue injury, suggesting a role for these modulators in both pain and inflammation. Contrary to our hypothesis, the histologic findings (eg, axons and blood vessels) failed to show a correlation with the clinical presence of anterior shoulder pain. Furthermore, immunohistochemical evaluation with anti-CGRP and anti-substance P antibodies failed to show a difference between LHBB tendons of the surgical and control samples.

Both proteins were largely present throughout the entire tissue section, with the highest accumulation in the axon bundles and blood vessels. Additional immunohistochemistry with a different anti-CGRP antibody showed the same pattern of staining and protein distribution as with the first antibody, confirming the specificity of the immunostaining. Localization of substance P and CGRP within the cervical spinal cord, as reported in the literature, thus served as a positive control for the immunohistochemistry of the biceps tendon.²⁶ Numerous studies have used cadaveric tissues as controls because of the difficulty in obtaining normal tissues of reasonable size from living subjects.^{6,11,14,23} In their histologic study of 891 spontaneous human tendon ruptures, Kannus and Jozsa¹³ used 445 cadaveric tissues for their control group. Zamboni's fixative, an antigen-preserving protocol, was used for tendon processing.^{1,28} The primary samples of interest, surgical specimens after tenodesis, were fixed immediately and processed for histology. It is unlikely that degradation or denaturation of these samples occurred. Coupled with the specific staining noted in both groups, the failure of the immunohistochemical staining to support the hypothesis is a valid result. The absence of differences between the surgical and cadaveric specimens may be attributed to a number of technical and principle reasons. It is possible that the LHBB tendon is not the sole cause of anterior shoulder pain in cuff-deficient shoulders and that a more complex interaction of the tendon with its surrounding sheath and soft tissue is more likely to be responsible.

Intrigued by the possible role of the biceps tendon sheath in chronic rotator cuff tears as a source of anterior shoulder pain, we analyzed the biceps tendon sheath in phase 2 of our study. Furthermore, we compared the results from clinical tests used for the diagnosis of biceps tendinitis (Yergason's and Speed's tests) with the histologic findings of clinically diagnosed biceps tendinitis. Interestingly, the results of this study did not show a significant difference in the grading scores for inflammation and vascularity between the clinical samples and the controls. There was also no significant correlation between the clinical tests by use of a binary scoring system (ie, positive or negative) and histologic scores for inflammation and vascularity. Interestingly, a moderate correlation between pain (scored on a scale from 0-10) and tendon vascularity was observed, but there was no correlation between pain and inflammation. Hence, the results of the selected clinical tests alone were poorly correlated with tissue assessments of biceps pathology. In addition, the arthroscopic findings were inconsistent with those of the clinical tests. These observations suggest that the use of imaging techniques, such as ultrasonography³⁴ or magnetic resonance imaging, to supplement clinical assessments of function and

pain may be needed to provide a more accurate diagnosis of biceps pathology.

Future immunohistochemical studies using other markers of pain and inflammation, such as bradykinin and its inducible receptor, interleukin 2, interleukin 3, and tumor necrosis factor α , may afford a more thorough evaluation of the presence of inflammation and hence improve our understanding of the role of the biceps tendon as a source of pain. The choice of these biomarkers is dictated by the notion that they are closely associated with the activation of pain-related neuromediators.

Interestingly, the histologic findings (eg, axons, blood vessels, and cellularity) showed no correlation to clinical examination findings of anterior shoulder pain. Quantitatively, less innervation and vascularization indicate that the source of pain does not reside in the LHBB tendon. Conversely, the tendon sheath of surgical specimens showed a trend toward increased vascularity and inflammation. We speculate that pain may result from the interaction of the tendon and the surrounding soft tissue, including the tendon sheath.

Limitations of this study include the limited sample size, differences in type and time of storage of the cadaveric and surgical specimens, and the selective immunohistochemical sampling. Statistical power was less than 60% for all of the quantitative comparisons conducted in this study. Power analysis showed that 40 specimens per group would be required to achieve 80% power. The patient population was heterogeneous in terms of their concurrent pathologies and duration of symptoms. Tendon histology was analyzed at proximal and distal locations sites, without exhaustive, sequential sampling of the entire tendon length. Furthermore, control specimens were obtained from cadaveric donors with unknown medical history rather than the patients' contralateral joint.

Our results indicate that neither the tendon nor the sheath of the LHBB tendon is the sole cause of anterior shoulder pain. Patients undergoing biceps tenodesis generally had variable concurrent pathologies and durations of symptoms. The natural history of bicipital pain is likely multifactorial and the result of both biochemical and mechanical factors, which are difficult to elucidate from a heterogeneous cohort. We speculate that the complex interaction between the tendon and its surrounding soft-tissue environment, including the tendon sheath, is a possible explanation for the pain. The inconsistency of clinical findings for biceps tendinitis through arthroscopic visualization may warrant the use of specific imaging studies for improved diagnosis of this condition.

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